

### REMARKS

Upon entry of this amendment, claims 70, 72, 74-76, and 78 will be pending in the application. Claims 70, 72, 74, and 76 are amended to provide clear antecedent basis. Claim 78 is added. Exemplary support for the claims is located in the specification at page 3, lines 15-18 and page 12, lines 15-21. Claims 1-69, 71, 73, and 77 are canceled.

Objections to claims 70 and 73 have been raised. Claim 73 is further rejected for alleged improper dependency. Without conceding the propriety of the objection and rejection and in an effort to advance prosecution of the application, claim 70 is amended to remove the term “PMS2-134” and to recite a “polynucleotide comprising a nucleotide sequence encoding the first 133 amino acids of PMS2.” Exemplary support for the amendment is located in the specification at pages 9, 13, 15, and 22. Claim 73 is canceled in view of the amendment to claim 70.

Claims 70 and 72-77 are rejected under section 112 for allegedly containing new matter. Applicants disagree. Exemplary support for the recitation of expression of a polynucleotide sequence of the mutated gene encoding the preselected immunogen in a genetically stable cell is located in the specification on page 3, lines 15-18 and page 12, lines 15-21. Withdrawal of the rejection is respectfully requested.

***The obviousness-type double patenting rejections should be withdrawn.***

Claims 70 and 72-77 were previously rejected in the Office Action mailed May 31, 2007 for alleged obviousness-type double patenting over claims 1-3 and 6 of U.S. Patent No. 6,825,038 in view of Parkhurst *et al.*, *J. Immunol.*, 1996, 2539-2548. Applicants erroneously submitted a terminal disclaimer over U.S. Patent No. 6,825,038. The terminal disclaimer was erroneous because the patent and the present application are not commonly owned. Applicants have submitted a Petition under 37 C.F.R. 1.182 to withdraw the erroneously filed terminal disclaimer. Claims 70 and 73-77 also are rejected for alleged obviousness-type double patenting over claims 7-13 and 16-18 of U.S. Patent No. 6,146,894 in view of Parkhurst *et al.*, *J. Immunol.*, 1996, 2539-2548. Applicants also traverse the rejections.

Claims 70, 72, 74-76, and 78 recite methods for making a genetically stable cell that produces a therapeutically hypermutated immunogen by introducing into a first cell that

expresses a gene encoding a preselected immunogen *in vitro* a polynucleotide comprising a nucleotide sequence encoding the first 133 amino acids of PMS2, wherein the expression product of the polynucleotide is capable of inhibiting mismatch repair; selecting cells that comprise a mutation in the gene encoding the preselected immunogen, wherein the mutation results in enhanced antigenicity or immunogenicity of the immunogen; and expressing a polynucleotide sequence of the mutated gene encoding the preselected immunogen in a second cell, wherein the second cell is genetically stable. Claim 77 recites cultures of such cells

The Office asserts that the Parkhurst reference teaches a selection step that would necessarily render cells expressing a preselected immunogen with enhanced antigenicity. (Office Action, page 6.) This assertion, however, is incorrect. The Parkhurst reference hypothesizes a relationship between immunogenicity and MHC-binding affinity for viral antigens. (Parkhurst reference, page 2538). Based on known relationships between peptide modifications and binding affinity, select mutations were introduced into viral antigens. (See Parkhurst reference, page 2540.) Modified viral antigens having increased binding affinity were selected as candidates for further evaluation of immunogenicity. In some cases, the selected candidates were demonstrated not to yield enhanced immunogenicity. (See, e.g., Parkhurst reference, page 2542.) One skilled in the art would not have predicted on the basis of the Parkhurst reference that inhibition of mismatch repair as taught by the claims of U.S. Patent Nos. 6,825,038 and 6,146,894, which generates genome-wide mutations, could effect mutations in antigens to increase antigenicity or immunogenicity in view of the teaching by the Parkhurst reference that select mutations in MHC-binding anchor positions of viral antigens associated with increased MHC-binding affinity may or may not also correlate to increased immunogenicity. Withdrawal of the rejection is requested.

***The obviousness rejections should be withdrawn.***

Claims 70 and 72-77 are rejected for alleged obviousness over Nicolaides *et al.*, *Mol. Cell. Biol.*, 1998, 18:1635-1641, in view of U.S. Patent No. 6,825,038, the Parkhurst reference, and Qin *et al.*, *Oncogene*, 1999, 18:4394-4400. Claims 70 and 72-77 are further rejected for alleged obviousness over U.S. Patent No. 6,146,894 in view of the Parkhurst and Qin references. Applicants disagree with the rejections.

Claims 70, 72, 74-76, and 78 recite methods for making a genetically stable cell that produces a therapeutically hypermutated immunogen by introducing into a first cell that expresses a gene encoding a preselected immunogen *in vitro* a polynucleotide comprising a nucleotide sequence encoding the first 133 amino acids of PMS2, wherein the expression product of the polynucleotide is capable of inhibiting mismatch repair; selecting cells that comprise a mutation in the gene encoding the preselected immunogen, wherein the mutation results in enhanced antigenicity or immunogenicity of the immunogen; and expressing a polynucleotide sequence of the mutated gene encoding the preselected immunogen in a second cell, wherein the second cell is genetically stable.

The Office asserts that the Parkhurst reference broadly teaches the usefulness of introducing mutations in wild-type antigens that result in increased antigenicity. (Office Action, pages 12 and 16.) This assertion, however, is incorrect. The Parkhurst reference hypothesizes a relationship between immunogenicity and MHC-binding affinity for viral antigens. (Parkhurst reference, page 2538). Based on known relationships between peptide modifications at MHC-binding anchor positions of viral antigens and binding affinity, select mutations were introduced into viral antigens. (See Parkhurst reference, page 2540.) Modified viral antigens having increased binding affinity were selected as candidates for further evaluation of immunogenicity. In some cases, the selected candidates were demonstrated not to yield enhanced immunogenicity. (See, e.g., Parkhurst reference, page 2542.) One skilled in the art would not have predicted on the basis of the Parkhurst reference that inhibition of mismatch repair, which generates genome-wide mutations, could effect mutations in antigens to increase antigenicity or immunogenicity in view of the teaching by the Parkhurst reference that select mutations in MHC-binding anchor positions of viral antigens associated with increased MHC-binding affinity may or may not correlate to increased immunogenicity. Withdrawal of the rejection is requested.

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**PATENT**

### **Conclusion**

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable Action is respectfully requested. The Office is invited to contact the undersigned at 215.564.8978 should any issues remain unresolved upon filing of the present reply.

Respectfully submitted,

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/ Felicity E. Groth /  
Felicity E. Groth  
Registration No. 47,042

Woodcock Washburn LLP  
Cira Centre  
2929 Arch Street, 12th Floor  
Philadelphia, PA 19104-2891  
Telephone: (215) 568-3100  
Facsimile: (215) 568-3439